

REMARKS

Applicant respectfully requests reconsideration. Claims 28, 31-35 and 37-47 were previously pending in this application. Claim 28 is amended herein. Withdrawn claims 34, 38, and 41 have been canceled. As a result, claims 28, 31-33, 35, 37, 39 40 and 42-47 are still pending for examination with claim 28 being an independent claim. No new matter has been added.

Rejection Under 35 U.S.C. 112

The rejection of claims 28, 31-33, 35, 37, 39 40 and 42-47 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement has been maintained.

The Office asserts that the claims are not enabled because the specification does not provide a teaching of which immune system deficiencies listed on pages 3-4 of the Office Action are due to the broad scope of cancers, viral infections or bacterial infections. (Office Action pages 3-5).

The pending claims are not directed to the treatment of diseases encompassed by the list presented on pages 3-4 of the Office Action. The term immune system deficiency is defined in the specification as follows:

“a disease or disorder in which the subject's immune system is not functioning in normal capacity *or* in which it would be useful to boost a subject's immune response for example to eliminate a tumor or cancer (e.g. tumors of the brain, lung (e.g. small cell and non-small cell), ovary, breast, prostate, colon, as well as other carcinomas and sarcomas) or a viral (e.g. HIV, herpes), fungal (e.g. *Candida* sp.), bacterial or parasitic (e.g. *Leishmania*, *Toxoplasma*) infection in a subject.”
(Page 11, emphasis added).

An immune system deficiency may be either a disorder in which the immune system is not functioning in a normal capacity or a disorder where inducing an immune response would be beneficial, such as cancer and infectious disease. The claims have been amended to clarify that Applicant is only claiming the latter type of immune system deficiency. The claims do not encompass the treatment of a disorder in which immune system is not functioning in a normal capacity, such as the disorders listed on pages 3-4 of the Office Action.

On page 6 of the Office Action, the Office describes arguments citing Gramzinski et al and Jeamwattanalert et al presented in the last response to Office Action. It is stated that “Applicants

now argue that the papers were cited to show the beneficial effects of CpG oligonucleotides in a parasitic infection. These papers are still not persuasive to overcome the instant rejection and are directed to subject matter not within the scope of the claims." Applicant disagrees with the characterization of the prior arguments.

In the Office Action dated August 22, 2007, the Office asserted that the treatment and prevention of parasitic infection such as malarial infection is unpredictable because the parasite hides within a cell. Solely, in order to rebut that rejection, Applicant presented the two papers as evidence that CpG oligonucleotides had in fact been used effectively in the treatment of parasitic infection. Applicant was not arguing that parasitic infection was within the scope of the claims or that such references demonstrated the enablement of the claimed invention. Rather the references were provided to rebut a statement made by the Office in a prior response.

The Office also asserted that the claims directed to cancer, viral infection and bacterial infection were very broad and that the data included in the specification as filed did not support the breadth of such claims. Additionally, the references previously cited by Applicant, Sfondrini et al and Krieg et al were dismissed as not being relevant because they were directed to a single cancer, were in mice, or did not encompass the claimed oligonucleotides.

Applicant's fundamental invention is directed to a class of molecules that are useful in the treatment of diseases such as cancer and infectious diseases. The instant invention is based at least in part on the discovery that the immune system detects bacterial DNA by the presence of unmethylated CpG nucleotides, which can be present in a wide variety of base contexts. Applicant was the first to recognize that synthetic oligonucleotides containing unmethylated CpG irrespective of their sequence or length could replicate these immune activating effects of bacterial DNA.

The pattern of immune response elicited by CpG oligonucleotides and described and exemplified in the specification is predictive of a utility of this class of molecules in the treatment of cancer and infectious disease. The invention relates to the discovery that immunostimulatory CpG oligonucleotides produce a systemic immune response in a subject that is useful in the treatment of cancer and infectious disease. Prior to the invention it had been known that certain types of infections and bacterial extracts trigger immune responses that can cause regression of cancers. Additionally, bacterial infections provoke a host immune response. The present invention is based

at least in part on the discovery that the immune stimulatory effects of bacterial DNA result from the presence of unmethylated CpG motifs, which, in contrast, are predominately methylated and thus non-stimulatory in vertebrate DNA. The immune system has thus evolved a defense mechanism against infection that is based on immune recognition of CpG motifs, which trigger a protective immune response. One aspect of the invention is the recognition that the same type of immune response that is triggered through this defense pathway can be directed against cancer or infections such as viral or bacterial infections, using synthetic oligonucleotides that mimic bacterial DNA. From this discovery of the mechanism of immune activation by bacterial DNA, the invention provides for the use of synthetic oligonucleotides containing these CpG motifs to induce a pattern of immune activation, which is capable of causing reduction in tumors and infections. Clinical trials involving administration of bacterial DNA to humans demonstrated positive effects in cancer patients. (See e.g., Tokunaga et al Jpn. J. Infect. Dis 52, 1-11, 1999.)

The invention relates to the discovery that a class of molecules having a common structural motif (a CpG dinucleotide) provokes an immune response and when administered to a subject results in an immune response useful in the treatment of cancer and infectious diseases. This class of oligonucleotides is described throughout the specification. Data is presented *in vitro* and *in vivo* using an adequate number of different CpG containing oligonucleotides to meet the enablement requirement for the claimed invention. The experiments demonstrated that the unmethylated CpG dinucleotide was the important component of the oligonucleotides by testing a number of control oligonucleotides in which the C was methylated or the C and/or G were replaced with other dinucleotides. The data in the application, including that represented in Tables 1-3, establishes that the unmethylated CpG is responsible for the immune stimulation.

One skilled in the art would recognize the utility of treating cancer and infection based on the disclosure and data provided in the instant patent application. The immune stimulation data presented in the specification were derived from the use of several CG oligonucleotides. Tables 1-3 describe immune stimulation of murine cells by at least 35 CG oligonucleotides. Tables 1-3 demonstrate that many different CG oligonucleotides are capable of activating murine B cells and inducing cytokine expression in murine cells *in vitro*. Further, Applicants have provided examples in the specification that show production of antibody in response to oligonucleotide stimulation

(Example 2), stimulation of B cells, natural killer (NK) cells and monocytic cells (Example 3 and Example 4), and production of IL-6 (Example 8) as well as other cytokines (IFN-gamma and IL-12.

In view of the data in the specification the skilled artisan would have expected that CpG containing oligonucleotides would have the ability to provoke an immune response. Although some oligonucleotides may work better than others, it is expected that in general CpG oligonucleotides are immunostimulatory under the appropriate conditions.

At the time the priority patent application was filed it was known in the art that induction of interferon- γ (IFN- γ), IL-12, and IL-6, as well as NK cell activation was useful in the treatment of cancer. The following summaries of references published prior to or around the priority date of the instant application describe the state of the art with respect to immune system activation and the treatment of cancer.

Trinchieri et al., Blood, V.84, December 15, 1994, p. 4008 is a review article describing IL-12 in the production of cytotoxic lymphocytes. Page 4021 describes the role of IL-12 in anti-tumor immunity. Specifically, it is taught that "studies using transplantable tumors in experimental animals have shown a dramatic affect of IL-12 in decreasing tumor growth and metastasis formation and in significantly delaying death. Systemic Daily Treatment (5 days per week) had a significant inhibitory affect on the growth of metastasis induced by intravenous injection of B16 melanoma cells and efficiently inhibited the growth of subcutaneously injected tumors, even when treatment was initiated two weeks after tumor inoculation. An inhibitory affect of IL-12 on tumor growth, with a greater than two-fold increase in survival of inoculated animals, was also observed with the reticulum cell sarcoma M5076 and with the renal cell adenocarcinoma renca. In this latter tumor, complete remission, especially with peritumoral injection of IL-12, was observed in some animals; reinjection of the renca cells in the "cured" animals resulted in delayed growth of the tumor, suggesting that IL-12 may induce a memory immune response against the tumor" (paragraph spanning 4021-4022, references omitted).

Brunda et al. Journal Leukocyte Biology, V.55, February 1994 is a review article describing IL-12. Pages 285-286 of Brunda et al. describe the use of IL-12 in vivo in numerous murine tumor models. It is taught that "a large body of experimental evidence has now been accumulated demonstrating that IL-12 has potent antimetastatic and antitumor activity in a number of murine

tumor models. The therapeutic activity of IL-12 has been observed in four of four murine metastasis models, including both pulmonary and hepatic metastases.” (page 285, first column, last paragraph).

U.S. Patent No. 4,883,662 issued on November 28, 1989, describes an in vivo method for increasing NK cells in the blood of cancer patients because such NK cells have known activity against tumor cells (abstract). In the summary of the invention it is taught that “it has been established that increasing such natural killer cells is an important component of the immune system, and that accordingly the present method should be a decided advantage in cancer treatment.”

Hayashi et al., Proceeding of the Japan Academy, Series B: Physical and Biological Sciences, 1994, 70, 205, describes immunotherapy for the treatment of cancer. The abstract teaches that immunotherapy with BCG-CWS results in IFN- γ induction. It is further taught that cancer patients experiencing IFN- γ induction and/or strong skin reaction survived for longer periods of time than those patients showing no IFN- γ induction, who died after a short period.

The relation between IFN γ and treatment of viral infections was studied by Morris et al. (Infection and Immunity, 1982, 35(2):533-536) who showed that IFN γ is produced from two human T-lymphoblastoid lines upon virus infection (see page 536, left column). Baumgarth et al. (Journal of Virology, 1994, 68(11):7575-7581) disclose that IFN γ has been identified as a key factor in immune responses to viral infections and demonstrated IFN γ production in response to influenza virus.

Woodworth and Simpson (Am. J Path., vol 142 (5): 1544-55 (1993) employed HPV-infected and non-infected cells and analyzed their lymphokine secretion profiles. The authors report that while normal cervical cells constitutively secreted IL-1 alpha, IL-1 beta, IL-1 RA, IL-6, IL-8, TNF-alpha, and GM-CSF, the HPV-infected cell lines “exhibited significant down-regulation of IL-1 beta, IL-6, TNF-alpha, IL-8, and GM-CSF” (page 1548, right column, 1st paragraph, Figure 3, and Table 1). The authors note in their discussion that “if the constitutive release of lymphokines is involved in maintaining normal immunocompetence in the cervical mucosa, then decreased secretion might provide a more favorable environment for persistence of HPV-infected cells” (page

1552, right column, 2nd paragraph). Thus, one skilled in the art would recognize that a drug useful for boosting such cytokines would be useful in the treatment of viral infection.

Consistently, in the abstract of Schneider (Genitourin. Med., 1993, vol 69 (3): 165-73) it is stated that the impaired cellular immune response upon genital HPV infection is characterized by depletion of T helper/inducer cells and/or Langerhans cells and impaired function of natural killer cells and/or the infected keratinocytes. Morris et al (Br J Obstet Gynecol, 1983, vol 90(5):412-20) studied wart virus infections with no evidence of cervical intraepithelial neoplasia and noted "a patchy reduction or total absence of Langerhans' cells in the epithelium" (page 415, left column, 2nd paragraph). Langerhans' cells are antigen-presenting cells derived from monocytes. There was also a "striking reduction in the number of T lymphocytes". Thus, one of ordinary skill in the art would recognize the therapeutic value of CpG in treating a viral infection such as papilloma virus infection.

The results obtained by Applicants *in vitro* and *in vivo* (i.e. immune stimulation) are correlated with the specific condition claimed (i.e. cancer and infection). The above described references were published prior to or around the priority date of the instant application. These references establish that one of skill in the art would have recognized the utility of a CpG containing oligonucleotide which is effective in inducing IL-12, IFN- γ and NK cell activation in a method of treating or preventing cancer and infectious disease in a subject. Thus, at the time of the invention the data presented in the specification would have been sufficient to demonstrate to one of skill in the art that unmethylated CpG oligonucleotides are useful in the treatment of these diseases.

The teachings with respect to Sfondiri et al and Krieg et al were dismissed. The post-filing references were not presented to demonstrate that every CpG oligonucleotide has been used in humans to treat cancer and infectious disease as a stand alone. Rather the references were presented as evidence that, as Applicant's specification set forth, CpG oligonucleotides in fact were demonstrated following the invention to be useful in treating cancers and infectious disease in a subject. The fact that one reference is limited only to a specific cancer and is in a mouse and the other is limited to one oligonucleotide in humans, doesn't diminish the evidentiary purpose of the references.

Thus, it is requested that the rejection be withdrawn.

Rejection Under 35 U.S.C. 112

Claims 28, 31-33, 35, 37, 39 40 and 42-47 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The Office asserts that the rejection is based on an introduction of new matter into the claim as a result of the phrase "immune system deficiency is due to a cancer, viral infection or a bacterial infection." The reason for the rejection is that the definition of immune system deficiency in the specification does not literally recite the limitation that the deficiency is *due to* cancer or infectious disease.

Although Applicant disagrees with the rejection, in order to advance prosecution, claim 28 has been amended to recite that the subject has a cancer, viral infection or bacterial infection.

However, in order to clarify the record, the phrase "immune system deficiency is due to a cancer, viral infection or a bacterial infection" is not new matter. As pointed out by the examiner, the specification on page 11 teaches that an "'immune system deficiency" shall mean a disease or disorder in which it would be useful to boost a subject's immune response for example to eliminate a tumor or cancer (e.g. tumors of the brain, lung (e.g. small cell and non-small cell), ovary, breast, prostate, colon, as well as other carcinomas and sarcomas) or a viral (e.g. HIV, herpes), fungal (e.g. Candida sp.), bacterial or parasitic (e.g. Leishmania, Toxoplasma) infection in a subject."

A person of ordinary skill would have understood, at the time the patent application was filed, that the immune system deficiency is due to the underlying disease. The *ipsis verbis* recitation of the phrase is not required to provide an adequate written description of the invention. (See for instance MPEP 2163 II(a)3(a).)¹ It is clear that the immune system deficiency is due to the underlying disease that it treated. The recited definition provides adequate support for the claimed language.

¹ "If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. See, e.g., *Vas-Cath*, 935 F.2d at 1563, 19 USPQ2d at 1116; *Martin v. Johnson*, 454 F.2d 746, 751, 172 USPQ 391, 395 (CCPA 1972) (stating "the description need not be in *ipsis verbis* [i.e., "in the same words"] to be sufficient")."

Double Patenting Rejection

Claims 28, 31-33, 35, 37, 39, 40, 42 and 43-46 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 36 of copending Application No. 10/787,737. It is requested that the provisional rejection be held in abeyance until an indication of allowable subject matter is received.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, the Director is hereby authorized to charge any deficiency or credit any overpayment in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 23/2825, under Docket No. C1039.70083US06.

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Respectfully submitted,

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